

IMPACT OF DELAY ON HIV-1 DYNAMICS OF FIGHTING A VIRUS WITH ANOTHER VIRUS

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ABSTRACT. In this paper, we propose a mathematical model for HIV-1 infection with intracellular delay. The model examines a viral-therapy for controlling infections through recombining HIV-1 virus with a genetically modified virus. For this model, the basic reproduction number \mathcal{R}_0 are identified and its threshold properties are discussed. When $\mathcal{R}_0 < 1$, the infection-free equilibrium E_0 is globally asymptotically stable. When $\mathcal{R}_0 > 1$, E_0 becomes unstable and there occurs the single-infection equilibrium E_s , and E_0 and E_s exchange their stability at the transcritical point $\mathcal{R}_0 = 1$. If $1 < \mathcal{R}_0 < R_1$, where R_1 is a positive constant explicitly depending on the model parameters, E_s is globally asymptotically stable, while when $\mathcal{R}_0 > R_1$, E_s loses its stability to the double-infection equilibrium E_d . There exist a constant R_2 such that E_d is asymptotically stable if $R_1 < \mathcal{R}_0 < R_2$, and E_s and E_d exchange their stability at the transcritical point $\mathcal{R}_0 = R_1$. We use one numerical example to determine the largest range of \mathcal{R}_0 for the local stability of E_d and existence of Hopf bifurcation. Some simulations are performed to support the theoretical results. These results show that the delay plays an important role in determining the dynamic behaviour of the system. In the normal range of values, the delay may change the dynamic behaviour quantitatively, such as greatly reducing the amplitudes of oscillations, or even qualitatively changes the dynamical behaviour such as revoking oscillating solutions to equilibrium solutions. This suggests that the delay is a very important fact which should not be missed in HIV-1 modelling.

1. Introduction. Human immunodeficiency virus (HIV) is a serious mortal lentivirus, which can cause acquired immunodeficiency syndrome (AIDS). Reports have known that many people are killed by AIDS every year, and yet, until today, there is no effective way to cure the AIDS. Thus, many scientists and researchers have been focusing on the study of controlling the infections. One of the approaches developed recently, offered by genetic engineering, is to use recombinant virus capable of controlling infections of HIV [15, 12]. Recently, Revilla and Garcia-Ramos established a 5-dimensional ordinary differential system to investigate the control of the infections by introducing a recombinant virus to fight the virus [13]. Later, this model was studied by Jiang *et al.* [6] in detail to show various bifurcation patterns and rich dynamics, as well as a control study given in [18] by introducing a constant injection rate of the recombinant virus to this model.

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A standard and classic in-host model for HIV infection can be described by the following differential equations:

$$\begin{aligned}\dot{x} &= \lambda - dx - \beta xv, \\ \dot{y} &= \beta xv - ay, \\ \dot{v} &= ky - pv,\end{aligned}\tag{1}$$

where $x(t)$, $y(t)$, $v(t)$ are the density of virus-free host cells, infected cells, and a pathogen virus, respectively, at time t . The production rate and death rate for the healthy cells are respectively λ and d . β is the constant rate at which a T-cell is contacted by the virus. It is also assumed that once cells are infected, they may die at a rate a due to the action of either the virus or the immune system, and each produces the pathogens at a rate k during their life which on average has length $1/a$.

In [13], a second virus is added into model (1) which may cause the infected cells to have a second infection, called double-infection, leading to a modified model as

$$\begin{aligned}\dot{x} &= \lambda - dx - \beta xv, \\ \dot{y} &= \beta xv - ay - \alpha wy, \\ \dot{z} &= \alpha wy - bz, \\ \dot{v} &= ky - pv, \\ \dot{w} &= cz - qw,\end{aligned}\tag{2}$$

where $w(t)$ and $z(t)$ are the recombinant (genetically modified) virus and double-infected cells. After the second virus is enrolled, once the cells which have been infected by the pathogens are infected again by the recombinant, they can be turned into double-infected cells at a rate αwy , where the recombinants are removed at a rate qw . The double infected cells die at a rate bz , and release recombinants at rate cz . Having established the model (2), the authors of [13] analyzed the structure of equilibrium solutions and presented some simulations. Later, in [6], the authors fully analyzed the stability of all three equilibrium solutions and bifurcations between these equilibria, as well as proved the existence of Hopf bifurcation. Further, in [18], the fifth equation of model (2) is modified as $\dot{w} = \eta + cz - qw$, where η is a control parameter to measure the injection rate of the recombinant, and then a complete dynamical analysis is given in this article, showing that increasing η is beneficial for controlling/eliminating the HIV virus [18].

In this paper, to further improve the model (2), we introduce a time lag into the model (2), since in real situation, time is needed for the virus to contact a target cell and then the contacted cells to become actively affected. This can be described by the eclipse phase of the virus life cycle. Moreover, we assume that the probability density that a cell still remains infected for τ time units after being contacted by the virus obeys an exponentially decay function. Therefore, following the line of [17, 19], model (2) can be modified to

$$\begin{aligned}\dot{x}(t) &= \lambda - dx(t) - \beta x(t)v(t), \\ \dot{y}(t) &= \beta e^{-a\tau} x(t-\tau)v(t-\tau) - ay(t) - \alpha w(t)y(t), \\ \dot{z}(t) &= \alpha w(t)y(t) - bz(t), \\ \dot{v}(t) &= ky(t) - pv(t), \\ \dot{w}(t) &= cz(t) - qw(t),\end{aligned}\tag{3}$$

where τ denotes the average time for a viral particle to go through the eclipse phase. Because the dimension of the system is higher than two, model (3) may exhibit some interesting dynamic behaviors (Hopf bifurcation, limit cycles and even

chaos), which would make the analysis of the system more complicated. Thus, the main goal of this paper focuses on dynamical behaviour of the system with delay, in particular, on equilibrium solutions and their bifurcations. More importantly, we want to find the impact of the delay on the dynamical properties.

The rest of this paper is organized as follows. In next section, for system (3) we will discuss the well-posedness of the solutions, equilibria and their stability. Also, in order to properly define biologically meaningful equilibria, the basic reproduction number \mathcal{R}_0 will be defined. In Sections 3, 4 and 5, we analyze the stability of the three equilibria: disease-free equilibrium E_0 , single-infection equilibrium E_s , and double-infection equilibrium E_d . It will be shown that E_0 is globally asymptotically stable for $0 < \mathcal{R}_0 < 1$, E_s is globally asymptotically stable for $1 < \mathcal{R}_0 < R_1$, where $R_1 > 1$ is a constant defined in terms of the system parameters, and E_d is asymptotically stable for $R_1 < \mathcal{R}_0 < R_h$, where R_h denotes a Hopf critical point from which a family of limit cycles bifurcate. A numerical example is present in Section 6 to demonstrate the theoretical predictions. Finally, conclusion and discussion are drawn in Section 7.

2. Well-posedness, boundedness of solutions, equilibria and basic reproduction number. Because of biological reasons, all variables in model (3) must be non-negative. Therefore, for any non-negative initial values, the corresponding solution must remain non-negative. We have the following result.

Theorem 2.1. *All solutions of system (3) remain non-negative, provided the given conditions are non-negative, and bounded.*

Proof. For convenience, let $X = C([- \tau, 0]; R^5)$ be the Banach space of continuous mapping from $[- \tau, 0]$ to R^5 equipped with the sup-norm. Let $\mathbf{x}(t) = (x(t), y(t), z(t), v(t), w(t))^T$ and $\mathbf{x}_t(\theta) = \mathbf{x}(t+\theta)$ for $\theta \in [- \tau, 0]$. By the fundamental theory of FDEs (see, e.g. [4]), for any initial condition $\phi \in X$ with $\phi \geq 0$, we know that there exists a unique solution $\mathbf{x}(t, \phi)$ satisfying $\mathbf{x}(\theta, \phi) = \phi(\theta)$, $\theta \in [- \tau, 0]$.

System (3) can be written as $\dot{\mathbf{x}}(t) = \mathbf{f}(\mathbf{x}_t)$, where

$$\mathbf{f}(\mathbf{x}_t) = \begin{pmatrix} \lambda - dx_t(0) - \beta x_t(0)v_t(0) \\ \beta e^{-a\tau} x_t(-\tau)v_t(-\tau) - ay_t(0) - \alpha w_t(0)y_t(0) \\ \alpha w_t(0)y_t(0) - bz_t(0) \\ ky_t(0) - pv_t(0) \\ cz_t(0) - qw_t(0) \end{pmatrix}.$$

It is easy to see that if any $\phi \in X$ satisfies $\phi \geq 0$, $\phi_i(0) = 0$ for some i , then $\mathbf{f}_i(\phi) \geq 0$. Therefore, according to Theorem 2.1 (on page 81) in [14] we know that $\mathbf{x}(t, \phi) \geq 0$ for all $t \geq 0$ in its maximal interval of existence if $\phi \geq 0$.

Next, to show the boundedness of the solution $(x(t), y(t), z(t), v(t), w(t))$, we define

$$B(t) = cke^{-a\tau} x(t) + cky(t + \tau) + ckz(t + \tau) + \frac{ac}{2}v(t + \tau) + \frac{bk}{2}w(t + \tau).$$

Then, the derivative of $B(t)$ with respect to time t along the solution of trajectory of system (3) is given by

$$\begin{aligned}
\left. \frac{dB(t)}{dt} \right|_{(3)} &= cke^{-a\tau} [\lambda - dx(t) - \beta v(t)x(t)] \\
&\quad + ck[\beta e^{-a\tau} v(t)x(t) - ay(t+\tau) - \alpha w(t+\tau)y(t+\tau)] \\
&\quad + ck[\alpha w(t+\tau)y(t+\tau) - bz(t+\tau)] \\
&\quad + \frac{ac}{2}[ky(t+\tau) - pv(t+\tau)] + \frac{bk}{2}[cz(t+\tau) - qw(t+\tau)] \\
&= cke^{-a\tau} \lambda - dcke^{-a\tau} x(t) - \frac{a}{2}cky(t+\tau) - \frac{b}{2}ckz(t+\tau) \\
&\quad - p\frac{ac}{2}v(t+\tau) - q\frac{bk}{2}w(t+\tau) \\
&\leq cke^{-a\tau} \lambda - mB(t) \begin{cases} < 0 & \text{for } B(t) > \frac{ck}{m}e^{-a\tau}, \\ > 0 & \text{for } B(t) < \frac{ck}{m}e^{-a\tau}, \end{cases}
\end{aligned}$$

where $m = \min\{d, \frac{a}{2}, \frac{b}{2}, p, q\}$. This implies that $B(t)$ is bounded, so are $x(t)$, $y(t)$, $z(t)$, $v(t)$ and $w(t)$. \square

Model (3) has three possible biologically meaningful equilibria: disease-free equilibrium E_0 , single-infection equilibrium E_s and double-infection equilibrium E_d , given below:

$$\begin{aligned}
E_0 &= \left(\frac{\lambda}{d}, 0, 0, 0, 0 \right), \\
E_s &= \left(\frac{ap}{\beta ke^{-a\tau}}, \frac{k\beta\lambda e^{-a\tau} - adp}{\beta ak}, 0, \frac{k\beta\lambda e^{-a\tau} - adp}{\beta ap}, 0 \right), \\
E_d &= \left(\frac{\lambda\alpha cp}{d\alpha cp + \beta bkq}, \frac{bq}{\alpha c}, \frac{q(\alpha\beta\lambda cke^{-a\tau} - \beta abkq - \alpha acdp)}{\alpha c(\beta bkq + \alpha cdp)}, \right. \\
&\quad \left. \frac{bkq}{\alpha cp}, \frac{\alpha\beta\lambda cke^{-a\tau} - \beta abkq - \alpha acdp}{\alpha(\beta bkq + \alpha cdp)} \right).
\end{aligned}$$

We define

$$\mathcal{R}_0 \triangleq \frac{\lambda}{d} \cdot \frac{\beta e^{-a\tau}}{a} \cdot \frac{k}{p} = \frac{k\beta\lambda}{adp} e^{-a\tau},$$

where $\frac{\lambda}{d}$ is the average number of healthy cells available for infection, $\frac{\beta e^{-a\tau}}{a}$ is the average number of host cells that each HIV virus infects, and $\frac{k}{p}$ is the average number of HIV viruses that an infected cell produces. Therefore, \mathcal{R}_0 is the basic reproduction number.

It is seen that the disease-free equilibrium is independent of the delay. If $\mathcal{R}_0 < 1$, E_0 is the only biologically meaningful equilibrium. If $\mathcal{R}_0 > 1$, there is another biologically meaningful equilibrium E_s (single-infection equilibrium). The double-infection equilibrium E_d exists (biologically meaningful) if and only if $R_d > 1$, where

$$R_d = \frac{\alpha\beta\lambda cke^{-a\tau} - \alpha acdp}{\beta abkq} = \frac{\alpha cdp}{\beta bkq} (\mathcal{R}_0 - 1).$$

Hence,

$$R_d > 1 \Leftrightarrow \mathcal{R}_0 > R_1, \quad \text{where } R_1 = 1 + \frac{\beta bkq}{\alpha cdp}.$$

Note that R_1 is independent of the delay.

3. Stability of the disease-free equilibrium E_0 . First, for the local stability of E_0 , we have the following theorem.

Theorem 3.1. *When $\mathcal{R}_0 < 1$, the disease-free equilibrium E_0 is locally asymptotically stable; when $\mathcal{R}_0 > 1$, E_0 becomes unstable and the single-infection equilibrium E_s occurs.*

Proof. The linearized system of (3) at the disease-free equilibrium E_0 is

$$\begin{aligned}\dot{x}(t) &= -dx(t) - \frac{\beta\lambda}{d}v(t), \\ \dot{y}(t) &= \beta e^{-a\tau} \frac{\lambda}{d}v(t-\tau) - ay(t), \\ \dot{z}(t) &= -bz(t), \\ \dot{v}(t) &= ky(t) - pv(t), \\ \dot{w}(t) &= cz(t) - qw(t),\end{aligned}$$

for which the characteristic equation is given by

$$(\xi + d)(\xi + b)(\xi + q) \left[\xi^2 + (a + p)\xi + ap - \frac{\beta\lambda k}{d}e^{-(a+\xi)\tau} \right] = 0.$$

Obviously, for the local stability of E_0 , it suffices to only consider the following equation

$$D_0(\xi) = \xi^2 + (a + p)\xi + ap - \frac{\beta\lambda k}{d}e^{-(a+\xi)\tau} = 0. \quad (4)$$

If $\mathcal{R}_0 > 1$, it is easy to show for real ξ that

$$D_0(0) = ap(1 - \mathcal{R}_0) < 0, \quad \lim_{\xi \rightarrow +\infty} D_0(\xi) = +\infty.$$

Hence, $D_0(\xi) = 0$ has at least one positive real root. Therefore, if $\mathcal{R}_0 > 1$, the infection-free equilibrium E_0 is unstable.

Next, consider $\mathcal{R}_0 < 1$. When $\tau = 0$, equation (4) becomes

$$\xi^2 + (a + p)\xi + ap - \frac{\beta\lambda k}{d} = 0. \quad (5)$$

In order for the two roots of (5) to have negative real part, it requires $ap - \beta\lambda k/d > 0$, which is equivalent to $\mathcal{R}_0|_{\tau=0} < 1$. Thus, all the roots of (5) have negative real part when $\mathcal{R}_0 < 1$. From [2], we know that all the roots of (4) continuously depend on τ . And the assumption

$$\limsup \left\{ \left| \frac{Q(\xi, \tau)}{P(\xi, \tau)} \right| : |\xi| \rightarrow \infty, \operatorname{Re}(\xi) \geq 0 \right\} < 1, \quad \text{for any } \tau, \quad (6)$$

could ensure that there are no roots existing in the infinity for equations in the form $P(\xi, \tau) + Q(\xi, \tau)e^{-\xi\tau} = 0$ (see [1]). Obviously, (6) holds here for (4), and hence $\operatorname{Re}(\xi) < +\infty$ for any root ξ of (4) when $\mathcal{R}_0 < 1$. As a result, for $\mathcal{R}_0 < 1$, the only possibility for the roots of equation (4) to enter into the right half plane is to cross the imaginary axis when τ increases. Thus, we define $\xi = i\varpi$, ($\varpi > 0$), to be a purely imaginary root of (4). Then we get

$$-\varpi^2 + i(a + p)\varpi + ap - \frac{k\beta\lambda}{d}e^{-(a+i\varpi)\tau} = 0. \quad (7)$$

Taking moduli of (7) gives

$$H_0(\varpi^2) = \varpi^4 + (a^2 + p^2)\varpi^2 + a^2p^2 - \left(\frac{k\beta\lambda}{d}e^{-a\tau} \right)^2 = 0.$$

Clearly, $H_0(\varpi^2)$ has no positive real roots if $\mathcal{R}_0 < 1$. Therefore, all the roots of (4) have negative real part if $\mathcal{R}_0 < 1$. \square

Further, for the global stability of E_0 , we have the following result.

Theorem 3.2. *If $\mathcal{R}_0 < 1$, the disease-free equilibrium E_0 is globally asymptotically stable, implying that none of the two virus can invade regardless of the initial load.*

Proof. We construct the following Lyapunov function:

$$\begin{aligned} V_0 = & \frac{e^{-a\tau}}{2} \left[x(t) - \frac{\lambda}{d} \right]^2 + \frac{\lambda}{d} y(t) + \frac{\lambda}{d} z(t) + \frac{a\lambda}{dk} v(t) + \frac{b\lambda}{cd} w(t) \\ & + \frac{\lambda\beta}{d} e^{-a\tau} \int_{t-\tau}^t x(\eta) v(\eta) d\eta. \end{aligned}$$

Using non-negativity of the solution and $\mathcal{R}_0 < 1$, the derivative of V_0 with respect to time t along the solution of system (3) can be expressed as

$$\begin{aligned} \left. \frac{dV_0}{dt} \right|_{(3)} = & e^{-a\tau} \left[x(t) - \frac{\lambda}{d} \right] [\lambda - dx(t) - \beta v(t)x(t)] \\ & + \frac{\lambda}{d} [\beta e^{-a\tau} x(t-\tau)v(t-\tau) - ay(t) - bz(t)] \\ & + \frac{a\lambda}{dk} [ky(t) - pv(t)] + \frac{b\lambda}{cd} [cz(t) - qw(t)] \\ & + \frac{\lambda\beta}{d} e^{-a\tau} [x(t)v(t) - x(t-\tau)v(t-\tau)] \\ = & -e^{-a\tau} \left[x(t) - \frac{\lambda}{d} \right]^2 [d + \beta v(t)] - \left[\frac{a\lambda}{dk} p - \frac{\lambda^2}{d^2} \beta e^{-a\tau} \right] v(t) - \frac{bq\lambda}{cd} w(t) \\ = & -e^{-a\tau} \left[x(t) - \frac{\lambda}{d} \right]^2 [d + \beta v(t)] - \frac{ap\lambda}{dk} (1 - \mathcal{R}_0) v(t) - \frac{bq\lambda}{cd} w(t) \\ \leq & 0, \end{aligned}$$

and the equality holds for $x = \frac{\lambda}{d}$, $v = w = 0$. Thus, by LaSalle's invariance principle [8], we conclude that E_0 is globally asymptotically stable. \square

4. Stability of the single-infection equilibrium E_s . From the analysis given in the previous section, we know that at the critical point $\mathcal{R}_0 = 1$, the disease-free equilibrium E_0 becomes unstable and bifurcates into the single-infection equilibrium E_s , which exists for $\mathcal{R}_0 > 1$. Thus, in order to study the stability of E_s , we assume $\mathcal{R}_0 > 1$ in this section. Similarly, for the local stability of E_s , we have the following result.

Theorem 4.1. *If $1 < \mathcal{R}_0 < R_1$, the single-infection equilibrium E_s is asymptotically stable; when $\mathcal{R}_0 > R_1$, E_s becomes unstable.*

Proof. The linearized system of model (3) at $E_s = (x_s, y_s, 0, v_s, 0)$ is

$$\begin{aligned} \dot{x}(t) &= -(d + \beta v_s)x(t) - \beta x_s v(t), \\ \dot{y}(t) &= \beta e^{-a\tau} [v_s x(t-\tau) + x_s v(t-\tau)] - ay(t) - \alpha y_s w(t), \\ \dot{z}(t) &= \alpha y_s w(t) - bz(t), \\ \dot{v}(t) &= ky(t) - pv(t), \\ \dot{w}(t) &= cz(t) - qw(t), \end{aligned}$$

with the corresponding characteristic equation given by $D_1(\xi)D_2(\xi) = 0$, where

$$\begin{aligned} D_1(\xi) &= \xi^2 + (b+q)\xi + bq - \frac{c\alpha(k\beta\lambda e^{-a\tau} - adp)}{\beta ak}, \\ D_2(\xi) &= \xi^3 + \left(a+p + \frac{k\beta\lambda}{ap}e^{-a\tau}\right)\xi^2 + \left[\frac{k\beta\lambda}{ap}e^{-a\tau}(a+p) + ap\right]\xi \\ &\quad + k\beta\lambda e^{-a\tau} - ap(\xi+d)e^{-\xi\tau}. \end{aligned}$$

First, note that $D_1(\xi)$ can be rewritten as

$$D_1(\xi) = \xi^2 + (b+q)\xi + bq(1 - R_d),$$

which indicates that $D_1(\xi) = 0$ has two roots with negative real part if and only if $R_d < 1$ (i.e. $\mathcal{R}_0 < R_1$), or one positive root and one negative if $R_d > 1$ (i.e. $\mathcal{R}_0 > R_1$). Therefore, if $\mathcal{R}_0 > R_1$, the single-infection equilibrium E_s is unstable.

For $D_2(\xi) = 0$, we rewrite it as

$$\xi^3 + a_2(\tau)\xi^2 + a_1(\tau)\xi + a_0(\tau) - (c_1\xi + c_2)e^{-\xi\tau} = 0, \quad (8)$$

where

$$\begin{aligned} a_2(\tau) &= a + p + \frac{k\beta\lambda}{ap}e^{-a\tau}, \quad a_1(\tau) = \frac{k\beta\lambda}{ap}e^{-a\tau}(a+p) + ap, \\ a_0(\tau) &= k\beta\lambda e^{-a\tau}, \quad c_1 = ap, \quad c_2 = apd. \end{aligned}$$

It is easy to see that $\xi = 0$ is not a root of (8) if $\mathcal{R}_0 > 1$, since

$$a_0(\tau) - c_2 = k\beta\lambda e^{-a\tau} - apd = apd(\mathcal{R}_0 - 1) > 0.$$

When $\tau = 0$, (8) becomes

$$\xi^3 + a_2(0)\xi^2 + (a_1(0) - c_1)\xi + a_0(0) - c_2 = 0. \quad (9)$$

Applying the Routh-Hurwitz criterion (see [3]), we know that all the roots of (9) have negative real part, because

$$\begin{aligned} a_2(0) &= a + p + \frac{k\beta\lambda}{ap} > 0, \\ a_1(0) - c_1 &= \frac{k\beta\lambda}{ap}(a+p) > 0, \\ a_0(0) - c_2 &= k\beta\lambda - apd = apd(\mathcal{R}_0|_{\tau=0} - 1) > 0, \end{aligned}$$

and

$$\begin{aligned} a_2(0)(a_1(0) - c_1) - (a_0(0) - c_2) &= \left(a + p + \frac{k\beta\lambda}{ap}\right) \frac{k\beta\lambda}{ap}(a+p) - (k\beta\lambda - apd) \\ &= \frac{k^2\beta^2\lambda^2}{a^2p^2}(a+p) + \frac{k\beta\lambda}{ap}(a^2 + ap + p^2) + apd > 0. \end{aligned}$$

Therefore, any root of (8) has negative real part when $\tau = 0$. As discussed in Section 3, we know that all the roots of equation (8) depend continuously on τ . Also, (6) holds for (8), and hence $\text{Re}(\xi) < +\infty$ if $D_2(\xi) = 0$. Then, the roots of equation (8) can only enter into the right half plane by crossing the imaginary axis when τ increases. Thus, we define $\xi = i\varpi$ ($\varpi > 0$) to be a purely imaginary root of (8), and then obtain

$$-i\varpi^3 - a_2(\tau)\varpi^2 + ia_1(\tau)\varpi + a_0(\tau) - (ic_1\varpi + c_2)e^{-i\varpi\tau} = 0,$$

Taking moduli of the above equation results in

$$\begin{aligned} H_s(\varpi^2) &= \varpi^6 + [a_2^2(\tau) - 2a_1(\tau)]\varpi^4 \\ &\quad + [a_1^2(\tau) - 2a_0(\tau)a_2(\tau) - c_1^2]\varpi^2 + a_0^2(\tau) - c_2^2 = 0. \end{aligned} \quad (10)$$

Since

$$\begin{aligned} a_2^2(\tau) - 2a_1(\tau) &= a^2 + p^2 + d^2\mathcal{R}_0^2 > 0, \\ a_1^2(\tau) - 2a_0(\tau)a_2(\tau) - c_1^2 &= d^2(a^2 + p^2)\mathcal{R}_0^2 > 0, \\ a_0(\tau)^2 - c_2^2 &= a^2p^2d^2(\mathcal{R}_0^2 - 1) > 0, \end{aligned}$$

all the coefficients of $H_s(\varpi^2)$ are positive. Then the function $H_s(\varpi^2)$ is monotonically increasing for $0 \leq \varpi^2 < \infty$ with $H_s(0) > 0$. This implies that equation (10) has no positive roots if $\mathcal{R}_0 > 1$. Hence, all the roots of (8) have negative real part for $\tau > 0$ if $\mathcal{R}_0 > 1$. \square

Also, we can show the global stability of E_s , as given in the following theorem.

Theorem 4.2. *If $1 < \mathcal{R}_0 < R_1$, the single-infection equilibrium E_s is globally asymptotically stable, implying that the recombinant virus can not survive but the pathogen virus can.*

Proof. We construct the Lyapunov function $V_s = V_1 + \beta x_s v_s e^{-a\tau} V_2$ with

$$\begin{aligned} V_1 &= e^{-a\tau}(x - x_s \ln x) + (y - y_s \ln y) + z + \frac{a}{k}(v - v_s \ln v) + \frac{b}{c}w, \\ V_2 &= \int_{t-\tau}^t \left(\frac{x(\eta)v(\eta)}{x_s v_s} - \ln \frac{x(\eta)v(\eta)}{x_s v_s} \right) d\eta. \end{aligned}$$

Substituting E_s into (3) yields three identities $G_i \equiv 0$, $i = 1, 2, 3$, where $G_1 = \lambda - dx_s - \beta x_s v_s$, $G_2 = \beta e^{-a\tau} x_s v_s - ay_s$, $G_3 = ky_s - pv_s$. Then we have

$$\begin{aligned} V_{1,x}\dot{x} &= V_{1,x}\dot{x} - e^{-a\tau} \left(1 - \frac{x_s}{x} \right) G_1 - \frac{v}{v_s} G_2 - \frac{av}{kv_s} G_3 \\ &= dx_s e^{-a\tau} \left(2 - \frac{x_s}{x} - \frac{x}{x_s} \right) + \beta x_s v_s e^{-a\tau} \left(1 - \frac{x_s}{x} - \frac{xv}{x_s v_s} \right) + \frac{ap}{k}v, \\ V_{1,y}\dot{y} &= V_{1,y}\dot{y} + G_2 \\ &= \beta x_s v_s e^{-a\tau} \left[1 + \frac{(y - y_s)x(t - \tau)v(t - \tau)}{yx_s v_s} \right] - ay + \alpha(y_s - y)w, \\ V_{1,v}\dot{v} &= V_{1,v}\dot{v} + \left(1 - \frac{yv_s}{y_s v} \right) G_2 + \frac{a}{k} G_3 = \beta x_s v_s e^{-a\tau} \left(1 - \frac{yv_s}{y_s v} \right) + ay - \frac{ap}{k}v, \\ V_{1,z}\dot{z} &= \alpha yw - bz, \quad V_{1,w}\dot{w} = bz - \frac{bq}{c}w, \end{aligned}$$

which yields

$$\begin{aligned} &V_{1,x}\dot{x} + V_{1,y}\dot{y} + V_{1,z}\dot{z} + V_{1,v}\dot{v} + V_{1,w}\dot{w} \\ &= \beta x_s v_s e^{-a\tau} \left[3 - \frac{x_s}{x} - \frac{yv_s}{y_s v} + \frac{(y - y_s)x(t - \tau)v(t - \tau)}{yx_s v_s} - \frac{xv}{x_s v_s} \right] \\ &\quad + dx_s e^{-a\tau} \left(2 - \frac{x_s}{x} - \frac{x}{x_s} \right) + \frac{\alpha dp}{\beta k}(\mathcal{R}_0 - R_1)w, \end{aligned} \quad (11)$$

where $y_s = \frac{dp}{\beta k}(\mathcal{R}_0 - 1)$ has been used. And for V_2 , we have

$$\frac{dV_2}{dt} = \frac{xv}{x_s v_s} - \frac{x(t - \tau)v(t - \tau)}{x_s v_s} + \ln \frac{x(t - \tau)v(t - \tau)}{xv}. \quad (12)$$

Combining (11) and (12) yields

$$\begin{aligned} \frac{dV_s}{dt} \Big|_{(3)} &= V_{1,x}\dot{x} + V_{1,y}\dot{y} + V_{1,z}\dot{z} + V_{1,v}\dot{v} + V_{1,w}\dot{w} + \beta x_s v_s e^{-a\tau} \frac{dV_2}{dt} \\ &= dx_s e^{-a\tau} \left(2 - \frac{x_s}{x} - \frac{x}{x_s} \right) + \frac{\alpha dp}{\beta k} (\mathcal{R}_0 - R_1) w + \beta x_s v_s e^{-a\tau} W, \end{aligned}$$

where

$$W = 3 - \frac{x_s}{x} - \frac{y v_s}{y_s v} - \frac{y_s x(t-\tau) v(t-\tau)}{y x_s v_s} + \ln \frac{x(t-\tau) v(t-\tau)}{x v} \leq 0,$$

because the following inequality

$$n - \sum_{i=1}^n \frac{b_i}{a_i} + \ln \prod_{i=1}^n \frac{b_i}{a_i} \leq 0,$$

holds for any positive a_i and b_i (see [7]). Therefore, $\frac{dV_s}{dt} \Big|_{(3)} \leq 0$ when $\mathcal{R}_0 < R_1$, and the equality holds when $x = x_s$, $y = y_s$, $v = v_s$, $w = 0$. Then, by LaSalle's invariance principle [8], we conclude that E_s is globally asymptotically stable. \square

5. Stability of the double-infection equilibrium E_d . At the critical point $\mathcal{R}_0 = R_1$, the single-infection equilibrium E_s becomes unstable and the double-infection equilibrium E_d comes into existence for $\mathcal{R}_0 > R_1$. To discuss the stability of E_d , we assume $\mathcal{R}_0 > R_1$ in this section. We have the following result for the stability of E_d .

Theorem 5.1. *For model (3), there exists an $R_2 > R_1$ such that the double-infection equilibrium E_d is asymptotically stable for $R_1 < \mathcal{R}_0 < R_2$.*

Proof. The linearized system of (3) at $E_d = (x_d, y_d, z_d, v_d, w_d)$ is

$$\begin{aligned} \dot{x}(t) &= -(d + \beta v_d)x(t) - \beta x_d v(t), \\ \dot{y}(t) &= \beta e^{-a\tau} [v_d x(t-\tau) + x_d v(t-\tau)] - (a + \alpha w_d)y(t) - \alpha y_d w(t), \\ \dot{z}(t) &= \alpha w_d y(t) - b z(t) + \alpha y_d w(t), \\ \dot{v}(t) &= k y(t) - p v(t), \\ \dot{w}(t) &= c z(t) - q w(t). \end{aligned} \tag{13}$$

By straightforward but tedious algebraic manipulations, we obtain the characteristic equation of (13), given by

$$\begin{aligned} D(\xi) &= (\xi + p)(\xi + d R_1) \left[\xi(\xi + b + q) \left(\xi + a \frac{\mathcal{R}_0}{R_1} \right) + a b q \left(\frac{\mathcal{R}_0}{R_1} - 1 \right) \right] \\ &\quad - a p \frac{\mathcal{R}_0}{R_1} \xi(\xi + d)(\xi + b + q) e^{-\xi \tau} \\ &= \xi^5 + \sum_{i=0}^4 A_i \xi^i - \sum_{i=1}^3 B_i \xi^i e^{-\xi \tau} = 0, \end{aligned} \tag{14}$$

where

$$\begin{aligned}
A_4 &= dR_1 + a\frac{\mathcal{R}_0}{R_1} + b + p + q, \\
A_3 &= (b + p + q)\left(dR_1 + a\frac{\mathcal{R}_0}{R_1}\right) + p(b + q) + ad\mathcal{R}_0, \\
A_2 &= ad(b + p + q)\mathcal{R}_0 + p(b + q)\left(dR_1 + a\frac{\mathcal{R}_0}{R_1}\right) + abq\left(\frac{\mathcal{R}_0}{R_1} - 1\right), \\
A_1 &= adp(b + q)\mathcal{R}_0 + abq(p + dR_1)\left(\frac{\mathcal{R}_0}{R_1} - 1\right), \\
A_0 &= abdpq(\mathcal{R}_0 - R_1), \\
B_3 &= ap\frac{\mathcal{R}_0}{R_1}, \quad B_2 = ap(b + d + q)\frac{\mathcal{R}_0}{R_1}, \quad B_1 = apd(b + q)\frac{\mathcal{R}_0}{R_1},
\end{aligned}$$

showing that all A_i ($i = 1, 2, 3, 4$) and B_j ($j = 1, 2, 3$) are positive for $\mathcal{R}_0 > R_1$.

When $\tau = 0$, it has been shown in [6] that there exists a constant $R_2^* > R_1$ such that E_d is locally asymptotically stable when $\mathcal{R}_0 \in (R_1, R_2^*)$, implying that all the roots of (14)| $_{\tau=0}$ have negative real part.

Obviously, $D(\xi)$ satisfies (6), which implies that $D(\xi) = 0$ has no roots in the infinity $\text{Re}(\xi) = +\infty$. Following the procedure as shown in Sections 3 and 4, we let $R(\varpi)$ and $S(\varpi)$ respectively be the real and imaginary part of $D(i\varpi)$ ($\varpi > 0$), given by

$$\begin{aligned}
R(\varpi) &= A_4\varpi^4 - A_2\varpi^2 + A_0 + B_2\varpi^2 \cos(\varpi\tau) + (B_3\varpi^2 - B_1)\varpi \sin(\varpi\tau), \\
S(\varpi) &= \varpi^5 - A_3\varpi^3 + A_1\varpi - B_2\varpi^2 \sin(\varpi\tau) + (B_3\varpi^2 - B_1)\varpi \cos(\varpi\tau).
\end{aligned}$$

Solving the equations $R(\varpi) = 0$ and $S(\varpi) = 0$ for $\sin(\varpi\tau)$ and $\cos(\varpi\tau)$, and then substituting the results into the identity, $\sin^2(\varpi\tau) + \cos^2(\varpi\tau) = 1$, yields

$$\frac{H(\varpi^2)}{(B_3\varpi^2 - B_1)^2\varpi^2 + B_2^2\varpi^4} = 0 \quad \Longleftrightarrow \quad H(\varpi^2) = 0,$$

where $H(\varpi^2) = \varpi^{10} + a_1\varpi^8 + a_2\varpi^6 + a_3\varpi^4 + a_4\varpi^2 + a_5$, with

$$\begin{aligned}
a_1 &= A_4^2 - 2A_3, \\
a_2 &= 2A_1 - 2A_2A_4 + A_3^2 - B_3^2, \\
a_3 &= 2A_0A_4 - 2A_1A_3 + A_2^2 + 2B_1B_3 - B_2^2, \\
a_4 &= A_1^2 - 2A_0A_2 - B_1^2, \\
a_5 &= A_0^2.
\end{aligned} \tag{15}$$

In what follows, we shall prove that there exists an $R_2 > R_1$ such that all the roots of $H(x) = 0$ have negative real part when $\mathcal{R}_0 \in (R_1, R_2)$, that is, there are no positive real roots for $H(\varpi^2) = 0$. Therefore, for $\mathcal{R}_0 \in (R_1, R_2)$, the roots of (14) stay in the left half complex plane and E_d is locally asymptotically stable.

The necessary and sufficient conditions for $\text{Re}(x) < 0$ when $H(x) = 0$ are given by

$$\begin{aligned}
\Delta_1 &= a_1 > 0, \\
\Delta_2 &= a_1a_2 - a_3 > 0, \\
\Delta_3 &= a_3\Delta_2 - a_1(a_1a_4 - a_5) > 0, \\
\Delta_4 &= a_4\Delta_3 - a_5[a_2\Delta_2 - (a_1a_4 - a_5)] > 0, \\
\Delta_5 &= a_5\Delta_4 > 0.
\end{aligned}$$

A straightforward calculation shows that

$$\Delta_1 = R_1^2 d^2 + a^2 \frac{R_0^2}{R_1^2} + p^2 + (b + q)^2 > 0,$$

for any positive parameter values. Obviously, $\Delta_5 = A_0^2 \Delta_4 > 0$ when $\Delta_4 > 0$.

For Δ_2 , Δ_3 and Δ_4 , it is not easy to determine their signs for general \mathcal{R}_0 . Hence, we take a continuity argument below. At $\mathcal{R}_0 = R_1$,

$$\begin{aligned} \Delta_2|_{\mathcal{R}_0=R_1} &= d^4(R_1^2 - 1)^2 F_1 + d^2(F_1^2 + 2d^2 F_1 - a^2 p^2)(R_1^2 - 1) \\ &\quad + [(b + q)^2 + d^2](a^2 + d^2 + p^2) F_1 > 0, \\ \Delta_3|_{\mathcal{R}_0=R_1} &= d^2[d^2(a^2 + p^2)R_1^4 + (a^4 + a^2 p^2 + p^4)R_1^2 + a^2 p^2] F_2 > 0, \end{aligned}$$

where

$$\begin{aligned} F_1 &= a^2 + p^2 + (b + q)^2 > 0, \\ F_2 &= d^2(F_1 - a^2)(F_1 - p^2)(R_1^2 - 1) + (b + q)^2[d^2 + (b + q)^2] F_1 > 0. \end{aligned}$$

and $\Delta_4|_{\mathcal{R}_0=R_1} = a^2 d^2 p^2 (b + q)^2 (R_1^2 - 1) \Delta_3|_{\mathcal{R}_0=R_1} > 0$. We know that Δ_i , $i = 2, 3, 4$, continuously depend on \mathcal{R}_0 . Hence, there exists an $R_2 \leq R_2^*$ such that Δ_i , $i = 2, 3, 4$, are all greater than zero if $R_1 < \mathcal{R}_0 < R_2$. \square

In [6], it is also proved that E_d could lose its stability through Hopf bifurcation when $\mathcal{R}_0|_{\tau=0}$ is far greater than R_1 . So when $\tau > 0$, Hopf bifurcation may occur from E_d if \mathcal{R}_0 is further increased from R_1 . To obtain the critical point at which a Hopf bifurcation takes place, we need solve the equations $R(\varpi) = 0$ and $S(\varpi) = 0$ for τ and ϖ , if we take τ as our bifurcation parameter. Then, we can determine the corresponding value(s) of \mathcal{R}_0 , and choose the smallest one R_h satisfying $R_h > R_1$. Denote by τ_h and ϖ_h the corresponding values of τ and ϖ .

Following [5], there are three additional conditions which need to be satisfied,

$$R(\varpi) = 0 \Rightarrow S(\varpi) \neq 0 \quad (\text{or } S(\varpi) = 0 \Rightarrow R(\varpi) \neq 0) \quad \text{for } R_1 < \mathcal{R}_0 < R_h, \quad (16)$$

$$\left. \frac{\partial D(\xi, \tau)}{\partial \xi} \right|_{\xi=i\varpi_h, \tau=\tau_h} \neq 0, \quad (17)$$

and

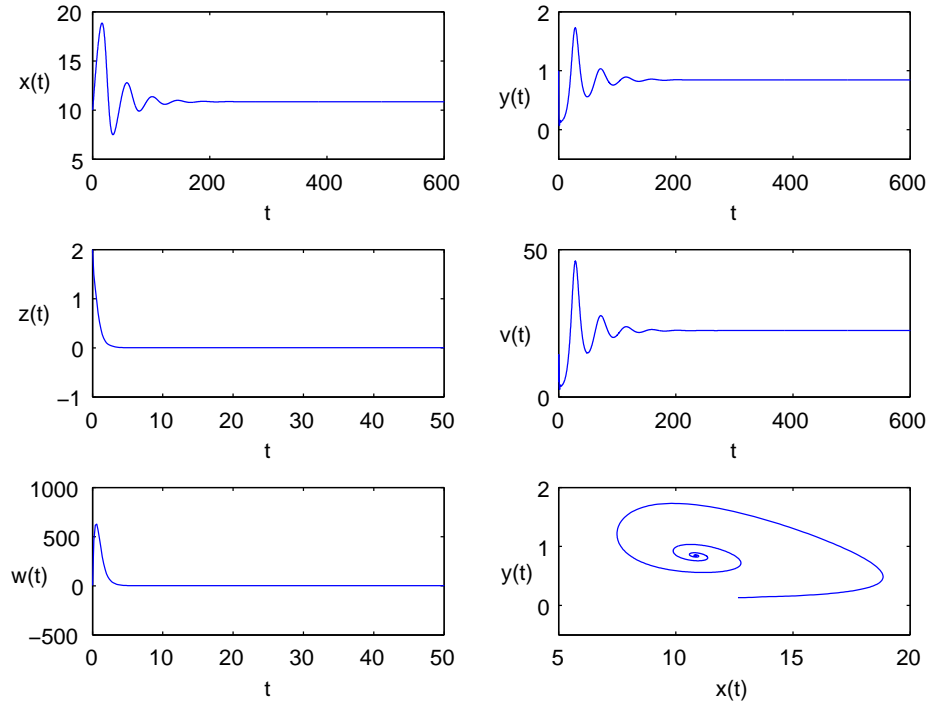
$$\left. \operatorname{Re} \left(\frac{d\xi}{d\tau} \right) \right|_{\xi=i\varpi_h, \tau=\tau_h} < 0. \quad (18)$$

The condition (16) implies that there are no solutions satisfying $R(\varpi) = S(\varpi) = 0$ if $\mathcal{R}_0 \in (R_1, R_h)$, for which the characteristic equation $D(\xi) = 0$ given in (14) does not have purely imaginary roots. From the proof of Theorem 5.1, we know that all roots of $D(\xi) = 0$ have negative real part for $\mathcal{R}_0 \in (R_1, R_h)$, which means that the equilibrium E_d is asymptotically stable if $R_1 > \mathcal{R}_0 < R_h$. If all the three conditions (16), (17) and (18) hold, we then conclude that (14) has a pair of purely imaginary roots and all other roots with negative real part at $\tau = \tau_h$ (i.e., at $\mathcal{R}_0 = R_h$), implying existence of a Hopf bifurcation. Therefore, at the critical point $\tau = \tau_h$, E_d loses its stability and bifurcates into a family of limit cycles.

6. Numerical Simulation. In this section, we present a numerical example and some simulations by using dde23 from the software MATLAB R2012a, to illustrate the theoretical results obtained in previous sections.

Table 1. Parameter notations and the sources for their values

| Definition | Value(day ⁻¹) | Source |
|--|----------------------------------|--------|
| λ Production rate of host cell | $0 \sim 10$ cell/mm ³ | [11] |
| d Death rate of host cell | 0.01 | [9] |
| β Infection rate of host cell by virus | 0.004 mm ³ /vir | [13] |
| a Death rate of HIV-1 infected cell | 0.5 | [11] |
| α Infection rate by recombinant | Assumed $\alpha = \beta$ | [13] |
| b Death rate of double-infected cell | 2 | [13] |
| k HIV-1 production rate by a cell | 50 vir/cell | [13] |
| p Removal rate of HIV-1 | 3 | [11] |
| c Production rate of recombinant by a double-infected cell | 2000 vir/cell | [13] |
| q Removal rate of recombinant | Assumed $q = p$ | [13] |

FIGURE 1. Simulation of system (3) for $\tau = 1.6 \in (\tau_2, \tau_1)$, showing convergence to the stable equilibrium E_s .

The notations and typical values of the parameters used in model (3) are given in Table 1. The precise value of τ is not obtained. But it is estimated that the value of τ is between $1.0 \sim 1.5$ days [11]. Here, we choose τ as the bifurcation parameter.

For computer simulation, we set $\lambda = 1$, $d = 1/180$, $\alpha = \beta = 1/260$, $a = 0.5$, $b = 2$, $p = q = 3$, $k = 80$, $c = 1800$. Then, $\mathcal{R}_0 = 480/13e^{-0.5\tau}$ and $R_1 = 17$. The disease-free equilibrium E_0 is now given by

$$E_0 = (180, 0, 0, 0, 0, 0),$$

which is globally asymptotically stable for $\tau > \tau_1 = 7.2176734929$, i.e., $\mathcal{R}_0 < 1$. When $\tau < \tau_1$, E_0 becomes unstable and the single-infection equilibrium E_s occurs, given by

$$E_s = \left(\frac{39}{8}e^{0.5\tau}, 2e^{-0.5\tau} - \frac{13}{240}, 0, \frac{160}{3}e^{-0.5\tau} - \frac{13}{9}, 0 \right),$$

which is globally asymptotically stable for $\tau_1 > \tau > \tau_2 = 1.5512468048$. See Figure 1 for the simulations of system (3) when $\tau = 1.6$.

Further decreasing τ to pass through the critical value τ_2 will cause E_s to lose its stability, giving rise to the double-infection equilibrium,

$$E_d = \left(\frac{180}{17}, \frac{13}{15}, \frac{8}{17}e^{-0.5\tau} - \frac{13}{60}, \frac{208}{9}, \frac{4800}{17}e^{-0.5\tau} - 130 \right).$$

The corresponding characteristic equation (14) at the above E_d becomes

$$\begin{aligned} D(\xi) = & \xi^5 + \left(\frac{240}{221}e^{-0.5\tau} + \frac{1457}{180} \right) \xi^4 + \left(\frac{5828}{663}e^{-0.5\tau} + \frac{709}{45} \right) \xi^3 \\ & + \left(\frac{15664}{663}e^{-0.5\tau} - \frac{19}{12} \right) \xi^2 + \left(\frac{4796}{221}e^{-0.5\tau} - \frac{557}{60} \right) \xi \\ & + \frac{24}{13}e^{-0.5\tau} - \frac{17}{20} - \left(\frac{720}{221}\xi^3 + \frac{212}{13}\xi^2 + \frac{20}{221}\xi \right) e^{-(\xi+0.5)\tau} = 0. \end{aligned} \quad (19)$$

Let $R(\varpi, \tau)$ and $S(\varpi, \tau)$ be the real and imaginary parts of $D(i\varpi)$ ($\varpi > 0$), yielding

$$\begin{aligned} R(\varpi, \tau) = & \left(\frac{240}{221}e^{-0.5\tau} + \frac{1457}{180} \right) \varpi^4 - \left(\frac{15664}{663}e^{-0.5\tau} - \frac{19}{12} \right) \varpi^2 + \frac{24}{13}e^{-0.5\tau} - \frac{17}{20} \\ & + \left(\frac{720}{221}\varpi^3 - \frac{20}{221}\varpi \right) e^{-0.5\tau} \sin(\varpi\tau) + \frac{212}{13}\varpi^2 e^{-0.5\tau} \cos(\varpi\tau), \\ S(\varpi, \tau) = & \varpi^4 - \left(\frac{5828}{663}e^{-0.5\tau} + \frac{709}{45} \right) \varpi^2 + \frac{4796}{221}e^{-0.5\tau} - \frac{557}{60} \\ & + \left(\frac{720}{221}\varpi^2 - \frac{20}{221} \right) e^{-0.5\tau} \cos(\varpi\tau) - \frac{212}{13}\varpi e^{-0.5\tau} \sin(\varpi\tau), \end{aligned}$$

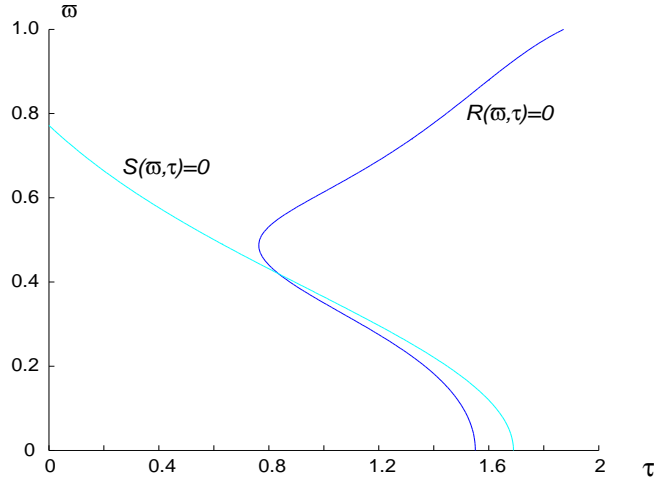


FIGURE 2. Plots of the curves $R(\varpi, \tau) = 0$ and $S(\varpi, \tau) = 0$ in the τ - ϖ plane with $(\varpi, \tau) \in [0, 2.1] \times [0, 2]$.

Solving the equations $R(\varpi, \tau) = 0$ and $S(\varpi, \tau) = 0$ by using the built-in command “fsolve” in Maple results in

$$(\tau_3, \varpi_3) = (0.8357983104, 0.4193565828).$$

Taking into account

$$\left(\frac{720}{221}\varpi^3 - \frac{20}{221}\varpi\right)\sin(\varpi\tau) + \frac{212}{13}\varpi^2\cos(\varpi\tau) \geq -\frac{4}{221}\sqrt{\varpi^2(32400\varpi^2 + 1)(\varpi^2 + 25)},$$

we have $R(\varpi, \tau) \geq \tilde{R}(\varpi)$, where

$$\begin{aligned} \tilde{R}(\varpi) = & \frac{4}{221} \left[60\varpi^4 - \frac{3916}{3}\varpi^2 + 102 - \varpi\sqrt{(32400\varpi^2 + 1)(\varpi^2 + 25)} \right] e^{-0.5\tau} \\ & + \frac{1457}{180}\varpi^4 + \frac{19}{12}\varpi^2 - \frac{17}{20}. \end{aligned}$$

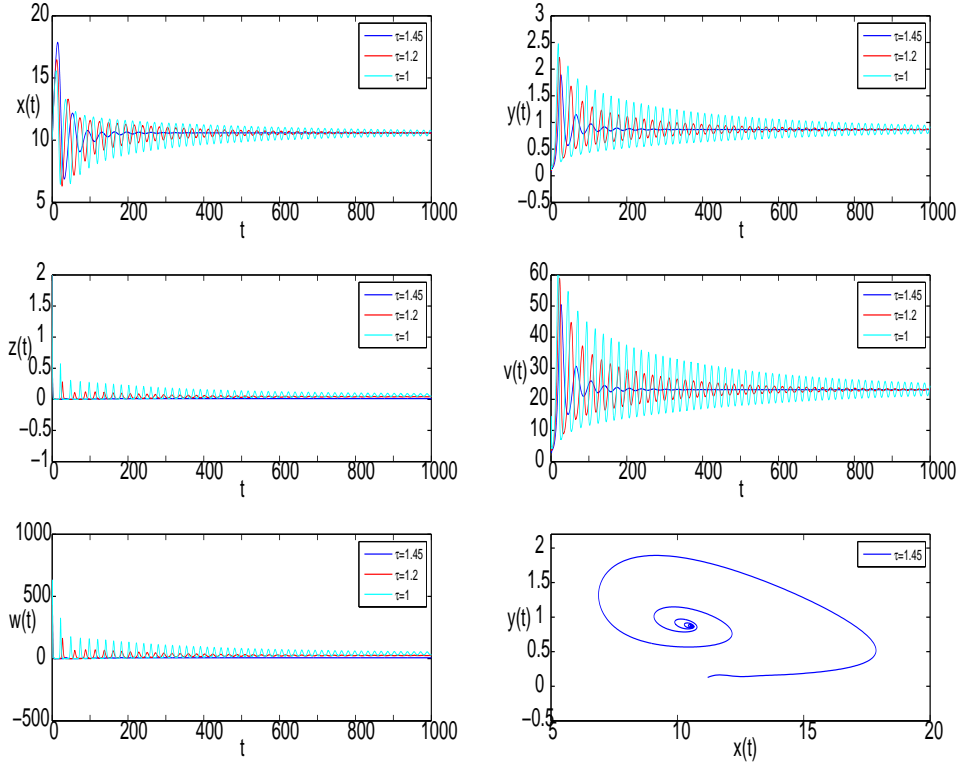


FIGURE 3. Simulation of system (3) for $\tau = 1.45, 1.2$ and 1.0 , taken from the interval $\tau \in (\tau_3, \tau_2)$, showing convergence to the stable equilibrium E_d .

It can be shown that for any $\tau > 0$, $\tilde{R}(\varpi) > 0$ if $\varpi > 2.1$. Thus, there are no roots of $R(\varpi, \tau) = 0$ for $\varpi > 2.1$, implying that the curve $R(\varpi, \tau) = 0$ in Figure 2 must be below the horizontal line $\varpi = 2.1$ (not shown in Figure 2), and so (τ_3, ϖ_3) is the only intersection point. Given that all the roots of (19) continuously depend on τ , it follows from Theorem 5.1 that E_d is asymptotically stable when $\tau_2 > \tau > \tau_3$. The simulations for $\tau = 1.45, 1.2$ and 1.0 are shown in Figure 3, from which we

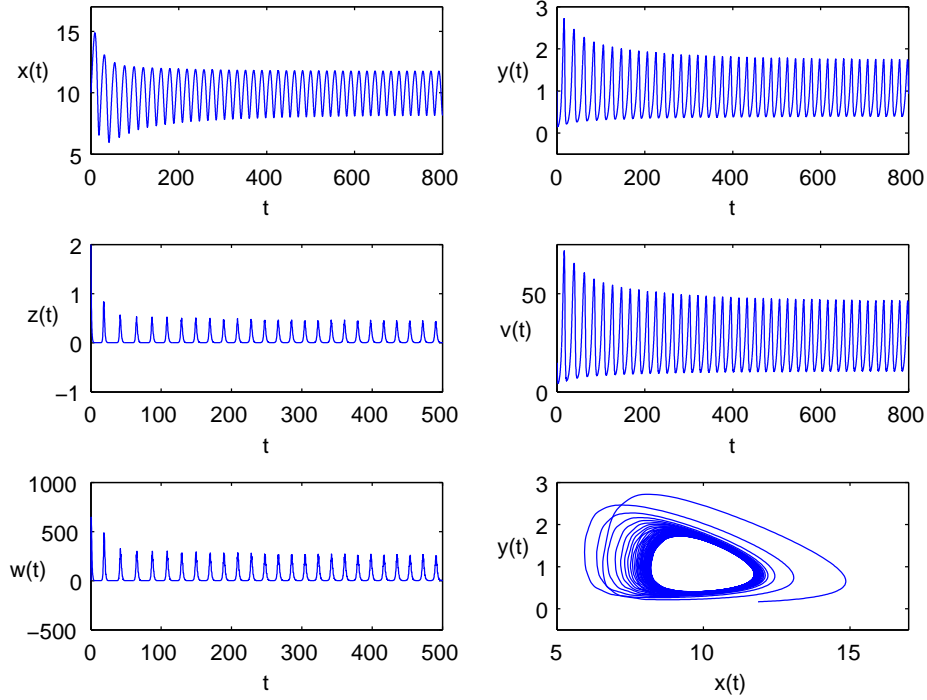


FIGURE 4. Simulation of system (3) for $\tau = 0.8 < \tau_3$, showing bifurcation to a stable limit cycle.

observe that all the components of a solution have more oscillating behaviors with larger amplitude, and they take longer time to converge to E_d when τ is decreased from τ_2 to τ_3 .

Finally, to consider possible Hopf bifurcation, first it is easy to see from Figure 2 that

$$S(\varpi, \tau) = 0 \implies R(\varpi, \tau) < 0, \quad \text{for } \tau_2 < \tau < \tau_3,$$

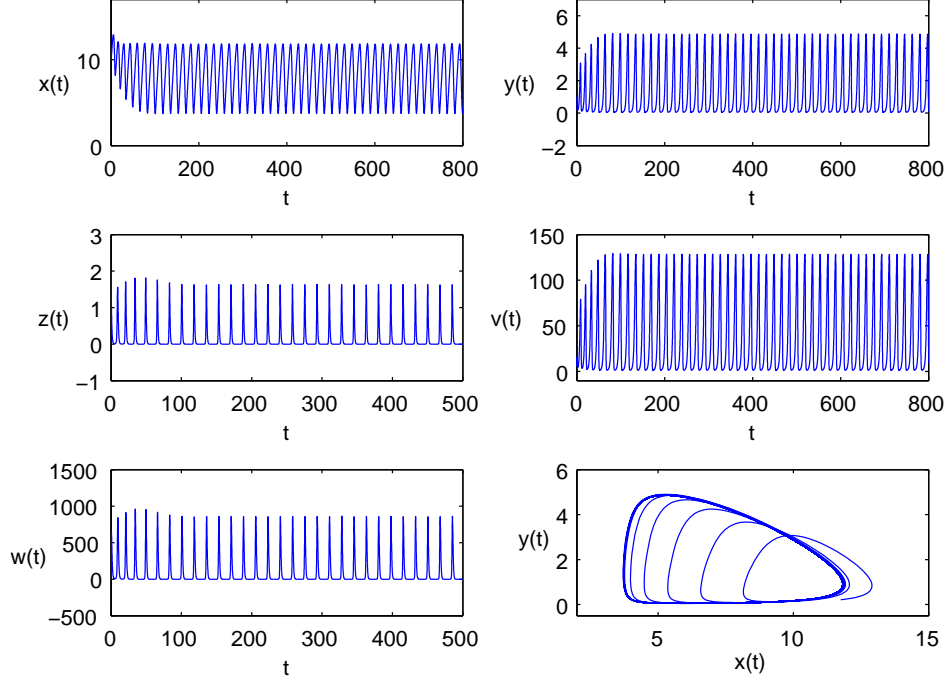
indicating that condition (16) is satisfied. Moreover, the other two conditions also hold:

$$\left. \frac{\partial D(\xi, \tau)}{\partial \xi} \right|_{\xi=i\varpi_3, \tau=\tau_3} = -9.8115344435 + 0.7314225159i \neq 0,$$

and

$$\operatorname{Re}\left(\frac{d\xi}{d\tau}\right) \Big|_{\xi=i\varpi_3, \tau=\tau_3} = -0.0137073586 < 0.$$

Thus, the roots of (19) have positive real part when $\tau < \tau_3$, and (19) has a pair of purely imaginary roots at $\tau = \tau_3$, implying existence of a Hopf bifurcation. Therefore, we conclude that when $\tau_2 > \tau > \tau_3$, the equilibrium solution E_d is asymptotically stable. At the critical point, $\tau = \tau_3$, E_d loses its stability through a Hopf bifurcation, giving rise to limit cycles. See the simulation shown in Figure 4. Further, the stability of limit cycles and the direction of bifurcations can be determined by using the center manifold theory and normal form theory for delay differential equations (e.g., see [16]). Detailed discussions on this part are out of the scope of this paper.

FIGURE 5. Simulation of system (3) for $\tau = 0$, showing oscillating behaviour.

In order to demonstrate the importance of the delay to be included in the model, in the following we will compare the results obtained above to that given at $\tau = 0$. It is easy to see that $\mathcal{R}_0|_{\tau=0} = \frac{480}{13} > R_1 = 17$, and thus both the disease-free equilibrium, E_0 , and the single-infection equilibrium, E_1 , are unstable when $\tau = 0$. To find the stability of the double-infection equilibrium, E_d , we set $\tau = 0$ in (19) to obtain

$$D(\xi) = \xi^5 + \frac{365197}{39780}\xi^4 + \frac{211709}{9945}\xi^3 + \frac{15209}{2652}\xi^2 + \frac{163463}{13260}\xi + \frac{259}{260},$$

which yields a purely pair and three negative eigenvalues: $0.03214833 + 0.76348925i$, -0.08306245 , -3.91260798 , and -5.24904353 , indicating that E_d is also unstable. Therefore, at $\tau = 0$, the system must exhibit oscillating behaviour, as shown in Figure 5. Comparing the results in this figure with that in Figure 4 shows that at $\tau = 0$, the solution trajectory converges much fast to reach its steady-state value than that in Figure 4 for $\tau = 0.8$. More importantly, it is noted that the amplitudes of the oscillations in Figure 5 is almost double of that in Figure 4 though their frequencies are almost not changed. The above observation shows that lack of even small delay in model (2) can cause significant quantitative changes in solutions. Moreover, for normal values of delay, the model (3) with delay can exhibit qualitatively different behaviour, compared with the model (2) without delay. For example, at $\tau = 1.2$ days, which is within the normal range of delays $\tau \in (1.0, 1.5)$ days [11], model (3) shows convergence to the stable double-infection equilibrium E_d , see Figure 3. At the marginal normal value $\tau = 1.6$, model (3) gives the stable single-infection equilibrium E_s , see Figure 1. These significant qualitative changes

due to existence of delay can not be observed from the model (2) without delay involved. This indeed suggests that the delay is a very important fact which should not be missed in model (2).

7. Conclusion and discussion. In this paper, we present a more realistic HIV-1 model of fighting a virus with another virus by adding delay to the model. The detailed analytic study has shown that the improved model with delay, like the model without delay, also has three equilibrium solutions: the disease-free equilibrium E_0 , single-infection equilibrium E_s , and double-infection equilibrium E_d , and a series of bifurcations occur as the basic reproduction number, \mathcal{R}_0 , is increased. It has shown that E_0 is globally asymptotically stable for $\mathcal{R}_0 \in (0, 1)$, and becomes unstable at the transcritical bifurcation point $\mathcal{R}_0 = 1$, and bifurcates into E_s , which is globally asymptotically stable for $\mathcal{R}_0 \in (1, R_1)$. E_s loses its stability at the another transcritical bifurcation point $\mathcal{R}_0 = R_1$, and asymptotically stable for $\mathcal{R}_0 \in (R_1, R_h)$. Finally, E_d becomes unstable at the Hopf critical point $\mathcal{R}_0 = R_h$, and bifurcates into a family of limit cycles.

When the delay is chosen as the bifurcation parameter, it is shown that the delay plays an important role in determining the dynamic behaviour of the system. In the normal range of values, the delay may change the dynamic behaviour quantitatively, such as greatly reducing the amplitudes of oscillations, or even qualitatively changes the dynamical behaviour such as revoking oscillating solutions to equilibrium solutions. This indeed suggests that the delay is a very important fact which should not be missed in HIV-1 modelling.

In this paper, only Hopf bifurcation has been considered. It is interesting to know whether the model can exhibit double Hopf bifurcation if, besides the delay, one more system parameter is chosen as second bifurcation parameter. Another interesting question arises if we include another fact of delay to model (3), that is, the existence of virus production period for new virions to be produced within and released from the infected cells (see [10]). When this second delay is included, model (3) becomes

$$\begin{aligned}\dot{x}(t) &= \lambda - dx(t) - \beta x(t)v(t), \\ \dot{y}(t) &= \beta e^{-a\tau_1} x(t - \tau_1)v(t - \tau_1) - ay(t) - \alpha w(t)y(t), \\ \dot{z}(t) &= \alpha w(t)y(t) - bz(t), \\ \dot{v}(t) &= ke^{-\tilde{a}\tau_2} y(t - \tau_2) - pv(t), \\ \dot{w}(t) &= cz(t) - qw(t),\end{aligned}\tag{20}$$

where τ_1 and τ_2 represent the latent period and virus production period, respectively. Then for this model, future work includes the study on the dynamical behaviour and bifurcation patterns of the model, and how the two delays influence stability and bifurcations. More interestingly, with these two delays as bifurcation parameters, can the model exhibit double Hopf bifurcation? Studying these questions will help to well understand the impact of delays on dynamical behaviour of HIV-1 model.

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